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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,461	03/02/2001	Esteban Cvitkovich	13566.105002	9636

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/787,461	CVITKOVICH ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 28-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 28-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response, filed 11/7/2008, is acknowledged and entered. Applicant's claim amendments, filed 4/7/2008, are entered in light of the Request for Continued Examination filed 11/7/2008. Claims 13-17 and 24-27 have been cancelled by Applicant. Claims 36-52 are newly added. Claims 12 and 28-52 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/7/2008 has been entered.

Notice of Appeal

In light of the Request for Continued Examination under 37 C.F.R. 1.114, filed 11/7/2008, the Notice of Appeal filed 4/7/2008 is **moot**.

Priority

This application is a 371 of PCT/GB00/01857, filed 5/15/2000, and claims foreign priority to UK Application Nos. 9911183.3, filed 5/13/1999; 9911346.6, filed 5/14/1999; 99185354.0, filed 11/15/1999; 99270005.0, filed 11/15/1999; 9927106.6, filed 11/16/1999; and 0007637.2, filed 3/29/2000.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

The priority afforded the instant claims for prior art purposes has been discussed in previous Office Actions. In the Final Office Action mailed 11/9/2007, the Examiner indicated that no support was found in the prior-filed foreign applications for the range "about 500 to about 1650 micrograms/m2 body surface area". Applicants have amended independent claim 12 to recite the limitation "...at a dose level of 1500 micrograms/m^2 body surface area....", support for

which is found in UK Application Nos. 9911183.3, filed 5/13/1999 (page 3, Example), wherein patients were administered a dose of ET-743 of 1500 $\mu g/m^2$. Accordingly, claims 12, 28-29, 31-33, 36-37, 41, 45, and 48-49 are afforded the benefit of the UK Application No. 9911183.3 filing date of **5/13/1999**. However, Applicants are reminded that prior art filed more than one year prior to the filing of PCT/GB00/01857 is still applicable as prior art under 35 U.S.C. 102(b).

No support is found in the 9911183.3 or 9911346.6 applications for the following claim limitations:

Claims 30, 38-40, 42-44, and 50-52 – melanoma, colon stromal sarcoma, gastric stromal sarcoma, liposarcoma, breast cancer, ovarian cancer, or ocular melanoma;

Claims 34 and 46 – "a steroid analogue", "an anti-inflammatory agent", or "an anti-emetic drug"; and

Claims 35 and 47 – "dexamethasone".

Lack of Ipsis Verbis Support

Application No. 9911183.3 (5/13/1999) is void of support for the cancer types recited in claims 30, 38-40, 42-44, and 50-52 including melanoma, colon stromal sarcoma, gastric stromal sarcoma, liposarcoma, breast cancer, ovarian cancer, and ocular melanoma. It is noted that page 1 recites sarcomas and mesotheliomas, including osteosarcomas and soft tissue sarcomas, leiomyosarcomas, and fibrosarcomas.

Application No. 9911183.3 (5/13/1999) is void of support for the additional therapeutic agents recited in claims 34 and 46 including "a steroid analogue", "an anti-inflammatory agent", and "an anti-emetic drug". It is noted that pages 2-3 recite additional drugs a) to l) as recited in the instant claims.

Application No. 9911183.3 (5/13/1999) is void of support for additionally administering dexamethasone as recited in claims 35 and 47.

Lack of Implicit or Inherent Support

Section 2163 of the MPEP states: "While there is no *in haec verba* requirement, newly added claim limitation must be supported in the specification through express, implicit, or inherent disclosure".

Although the above statement is with respect to new claim limitations, the analysis is similar in determining conditions for receiving the benefit of an earlier filing date.

Application No. 9911183.3 (5/13/1999) recites osteosarcomas and soft tissue sarcomas, leiomyosarcomas, and fibrosarcomas. None of the phrases "melanoma", "colon stromal sarcoma", "gastric stromal sarcoma", "liposarcoma", "breast cancer", "ovarian cancer", or "ocular melanoma" were located in Application No. 9911183.3. Further, one would not recognize nor conclude the term "sarcoma" is specifically meant to refer to "melanoma", "colon stromal sarcoma", "gastric stromal sarcoma", "liposarcoma", "breast cancer", "ovarian cancer", or "ocular melanoma". As such, one would not conclude that Application No. 9911183.3 provides adequate support for the claims.

Application No. 9911183.3 (5/13/1999) is void of support for the administration of "a steroid analogue", "an anti-inflammatory agent", or "an anti-emetic drug" as combination therapy. It is noted that Application No. 9911183.3 provides a list of other drugs that might be used in combination with ET-743. This list provides explicit support for items a) to l) in claims 34 and 46. None of the phrases "a steroid analogue", "an anti-inflammatory agent", or "an anti-emetic drug" were located in Application No. 9911183.3. Further, one would not recognize or conclude from the list of drugs provided in Application No. 9911183.3 that "additional drug" is meant to refer to "a steroid analogue", "an anti-inflammatory agent", or "an anti-emetic drug". As such, one would not conclude that Application No. 9911183.3 provides adequate support for the claims.

Application No. 9911183.3 (5/13/1999) is void of support for the administration of "dexamethasone" as combination therapy. It is noted that Application No. 9911183.3 provides a list of other drugs that might be used in combination with ET-743. This list provides explicit support for items a) to l) in claims 34 and 46. The drug "dexamethasone" is not mentioned in the disclosure of Application No. 9911183.3 and one would not recognize or conclude from the list of drugs provided in Application No. 9911183.3 that "additional drug" is meant to refer to "dexamethasone". As such, one would not conclude that Application No. 9911183.3 provides adequate support for the claims.

It is noted that section 706.02 VI C of the MPEP sets forth the method to determine the effective filing date. In particular, "If the application claims foreign priority under 35 U.S.C. 119(a)-(d) or 365(a) or (b), the effective filing date is the filing date of the U.S. application, unless situation (A) or (B) as set forth above applies. The filing date of the foreign priority

document is not the effective filing date, although the filing date of the foreign priority document may be used to overcome certain references". In the instant case, claims 30, 34-35, 38-40, 42-44, 46-47, and 50-52 are not fully supported by the foreign priority Application No. 9911183.3. As such, these claims do not receive the benefit of the foreign priority application. It is noted that claims are either fully supported or not fully supported. In other words, claims are not treated as 'supported in part' even though one particular element may be supported in the foreign-filed application.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Response to Arguments

Any previous rejections and/or objections to claims 13-17 and 24-27 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 11/7/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Specification

The previous objections to the disclosure set forth in the Final Office Action mailed 11/9/2007 are **withdrawn** in light of Applicant's cancellation of claim 15 and amendments to claim 12.

Claim Rejections - 35 USC § 112 – 2nd Paragraph – New Ground of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 12-17 and 24-35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding the limitation "about", is **withdrawn** in light of Applicant's amendments.

Claims 34 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 34 and 46 recite the limitation, "...a drug *potentially* affecting metastasis of tumors..." in line 5 of each respective claim. This limitation renders the claims unclear with respect to whether the drug does or does not affect the metastasis of tumors. For example, all drugs could "potentially" affect the metastasis of tumors, however only certain drugs actually do affect the metastasis of tumors. Further, it is not clear what is meant by "affecting" metastasis. Applicants do not define what is meant by this term and one skilled in the art could reasonably interpret "affecting metastasis" to mean inhibiting metastasis or accelerating metastasis. As such, the metes and bounds of the claims are unclear because it is not readily apparent what drugs are encompassed by this claim limitation (i.e., whether a drug does or does not affect metastasis and if a drug affects metastasis, what effect the drug has on metastasis).

Claim Rejections - 35 USC § 112 – 1st Paragraph – New Ground of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claim 14 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is **withdrawn** in light of Applicant's cancellation of claim 14.

Claims 34 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method comprising administering to a subject Ecteinascidin-743 and at least one additional drug, wherein the drug may be selected from "...a bioactive drug of marine origin...".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic genus, *i.e.*, generic bioactive drugs of marine origin.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43

USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is one species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* aplidine (page 9). The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a generic genus of compounds, *i.e.*, generic bioactive drugs of marine origin. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102 – New Ground of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 28-30, 32, 36, and 39-40 are rejected under 35 U.S.C. 102(b) as being anticipated by **Cvitkovich *et al***. (Annals Oncology, Abstract 456, 1998).[1]

Cvitkovich *et al*. teach that a clinical and pharmacokinetic study of ET-743 in solid advanced stage tumors has been ongoing since 1996. The drug was administered by continuous *i.v.* infusion for 24 hours given every 21 days at doses of 50-1500 $\mu g/m^2$ to 26 patients having cancer, thus meeting the limitations of claims 12 and 28-29.

Tumors types included colo-rectum, ovary, sarcoma, renal, breast, bladder, larynx, gastric, and ACUP, all refractory to standard therapy, thus teaching the limitations of claims 30, 32, 36, 39, and 40.

The Examiner acknowledges that table provided in the reference which discloses the transaminase levels resulting from administration of the 1500 mg/m2 dose level to four patients could be interpreted to mean that *only* four patients were administered this dose level. If such were the case, one could not say with certainty that one or more of these four patients had a cancer recited in claims 30, 32, or 39-40. However, in the absence of evidence to the contrary, the Examiner is interpreting the treatment of 26 patients "over 8 dose levels (50-1500 $\mu g/m^2$)" to mean that all patients were administered all dose levels, and only four patients administered the 1500 $\mu g/m^2$ dose level were measured for transaminase activity.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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[1] The date of Cvitkovich as recited in Applicant's IDS is only listed as "1998". The Examiner has been unable to determine the exact date this reference was available to the public. However, in light of the fact that the earliest effective U.S. filing date of the instant application is 5/15/**2000**, the month and day in 1998 the reference was available to the public are inconsequential because even if the reference was publicly available on 12/31/1998, it would still qualify as prior art under 35 U.S.C. 102(b).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Taamma *et al***. (Eur. J. Cancer, 1997, vol. 33, Suppl. 8, S247-248) and **Riofrio *et al***. (23rd European Society for Medical Oncology Congress, Nov. 6-10, 1998, Abstract 639P) in view of **Goodman and Gilman**.

Taamma teaches cyclic intravenous administration of ET-743 for the treatment of various tumors, such as breast, bladder, larynx, ovary, rectum, renal, gastric, and ACUP, all refractory to standard chemotherapy. ET-743 was administered for an infusion time of 24 hours every 3 weeks. Taamma teaches dose levels of 50, 100, 200, and 400 $\mu g/m^2$, which are outside the claimed dose of 1500 $\mu g/m^2$.

However, Riofrio teaches an ET-743 dosage range of 600-1800 $\mu g/m^2$, specifically a dose of 1500 $\mu g/m^2$, administered as a continuous *i.v.* infusion for 24 hours every 21 days for the treatment of advanced stage solid tumors such as colo-rectum, ovary, sarcoma, renal, breast, bladder, larynx, gastric, and SCUP cancers. "Advanced stage" tumors would reasonably include those tumors that are metastatic as recited in claim 31.

With regard to the administration of at least one additional drug such as an anti-emetic drug as recited in claims 34 and 46, Goodman and Gilman teach that dexamethasone is effective as an antiemetic in cancer chemotherapeutic regimens (Tables on page 930). It is noted that nausea and vomiting are disclosed in Riofrio as a side effect of ET-743 therapy at doses above 600 $\mu g/m^2$ and Taamma teaches that grade 1 emesis was seen in some patients undergoing ET-743 therapy.

In light of the above cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered ET-743 at a dose

level of 1500 micrograms/m^2 body surface area in cycles by intravenous infusion at an interval of 3 weeks with an infusion time of 24 hours as recited in the instant claims. The skilled artisan would have been motivated to do so because Taamma and Riofrio *et al*. both teach that ET-743 is a chemotherapeutic agent useful in the treatment of the claimed cancers that was being evaluated in Phase I clinical trials for the treatment of cancer prior to Applicant's invention. As such, Applicant's claimed methods of treating cancer by administering ET-743 using the claimed administration regimen would have been obvious to one skilled in the art.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that none of the cited references teach that the treatment results in a reduction in tumor size. In response, while the cited references do not disclose the results of the treatment methods taught therein, the *same* compound is administered in the *same* dose and in the *same* regimen as that recited in the instant claims. As such, it follows that the results of the treatment methods will be the same as those observed by Applicants. In other words, the Examiner is not persuaded that administration of the *same* compound to the *same* patients in the *same* dose and in the *same* manner as that claimed will not result in a reduction in tumor size. Applicants are reminded that the limitation "reduction in tumor size" does not require an observable reduction in tumor size.

Claims 41-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Taamma *et al***. and **Riofrio *et al***. in view of **Goodman and Gilman** as applied to claims 12 and 28-40 above, and further in view of **Holmes** (Seminars in Oncology, 1996, vol. 23, no. 5, pages 46-56) (cited in IDS filed 4/7/2008).

Taamma *et al*., Riofrio *et al*., and Goodman and Gilman teach as applied *supra* and are herein applied in the same manner in their entirety. Claim 41-52 differ from Taamma *et al*., Riofrio *et al*., and Goodman and Gilman in that the references do not disclose a 4 week cycle.

However, Holmes teaches that modification of existing chemotherapeutic regimens is routine in the art. For example, based upon the results of a Phase I trial of combination chemotherapy administered every 3 weeks, investigators adjusted doses and infusion times and modified the regimen to repeat the course every 4 weeks (page 49). As such, *i.v*. administration

of chemotherapeutic agents in 4 week cycles was clearly known in the art at the time the invention was made.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have optimized the dosing regimen of the cited prior art by adjusting the cycle time of drug administration. One skilled in the oncology art would have been motivated to seek an optimal dosing regimen for ET-743 with respect to dosages, infusion times and intervals of administration through no more than routine experimentation. It is clear from the prior art that the determination of an optimal dosing regimen depends on tumor type, the stage at which a diagnosis is made, the presence or absence of metastasis, prior therapy, the over-all condition of the patient and the avoidance of adverse drug effects, such as thrombopenia, neutropenia, acute renal failure and transaminitis.

Ample motivation to treat a human patient for cancer is provided for administering ET-743, optionally in combination with an additional drug, such as an antiemetic, with a reasonable expectation of success. In light of the fact that a 4 week administration cycle was known in the art at the time the invention was made and further in view of the fact that adjusting dosing schedules is well within the purview of the skilled artisan, Applicant's recited 4 week cycle is an obvious modification of the cited prior art. The skilled artisan would have been imbued with at least a reasonable expectation that administration of ET-743 in a 4 week cycle instead of the 3 week cycle disclosed in Riofrio *et al.* would be effective to treat cancer as recited in the instant claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12 and 28-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15, and 20-21 (6/10/2008 claim set) of copending Application No. 10/492,320 in view of **Riofrio *et al***. (23rd European Society for Medical Oncology Congress, Nov. 6-10, 1998, Abstract 639P) and **Holmes** (Seminars in Oncology, 1996, vol. 23, no. 5, pages 46-56). The claims of '320 are drawn a method of treating cancer comprising administering ET-743 in cycles by intravenous infusion with an infusion time of 3 hours with a dose of "about 580 $\mu g/m^2$/week" repeated weekly for 3 weeks every 4 weeks wherein the cancer is sarcoma, osteosarcoma, ovarian cancer, or breast cancer (claims 1 and 15) or melanoma, colorectal cancer, endometrial cancer, mesothelioma, or renal cancer (claims 20 and 21). The claims of '320 further recite use of additional drug such as dexamethasone. The instant claims differ from the '320 claims in the dose (1500 $\mu g/m^2$ versus "about 580 $\mu g/m^2$/week"), the infusion time (24 hours versus 3 hours) and in recitation of a 4 week interval.

However, Riofrio *et al*. teaches an ET-743 dosage range of 600-1800 $\mu g/m^2$, specifically a dose of 1500 $\mu g/m^2$ administered as a continuous *i.v*. infusion for 24 hours every 21 days for the treatment of advanced stage solid tumors such as colo-rectum, ovary, sarcoma, renal, breast, bladder, larynx, gastric, and SCUP cancers. "Advanced stage" tumors would reasonably include those tumors that are metastatic as recited in claim 31.

Holmes teaches that modification of existing chemotherapeutic regimens is routine in the art. For example, based upon the results of a Phase I trial of combination chemotherapy administered every 3 weeks, investigators adjusted doses and infusion times and modified the regimen to repeat the course every 4 weeks (page 49). As such, *i.v*. administration of

chemotherapeutic agents in 4 week cycles was clearly known in the art at the time the invention was made.

Accordingly, the claimed administration regimen would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. With respect to the specific cancers recited in the dependent claims, the skilled artisan would have been imbued with at least a reasonable expectation that administration of 1500 $\mu g/m^2$ ET-473 administered as a continuous *i.v.* infusion for 24 hours every 21 days or 28 days would be effective given the broad spectrum of cancers recited in '320 and Riofrio *et al.*

This is a provisional obviousness-type double patenting rejection.

Claims 12 and 28-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10, and 12-15 (12/3/2008 claim set) of copending Application No. 10/579,251 in view of **Riofrio *et al.*** (23rd European Society for Medical Oncology Congress, Nov. 6-10, 1998, Abstract 639P) and **Goodman and Gilman**. The claims of '251 are drawn a method of treating cancer comprising administering doxorubicin in a dose of about 50 mg/m^2 or about 60 mg/m^2 in combination with ET-743 in a dose range of between 0.6 and 0.75 mg/m^2 (i.e., 600 to 750 micrograms/m^2)(claim 1), wherein ET-743 is administered by intravenous infusion (claim 5), wherein the infusions are at an interval of 1 to 6 weeks (*e.g.*, once every 21 days or 28 days) (claims 8 and 9), and wherein the cancer is sarcoma, osteosarcoma, ovarian cancer, breast cancer, melanoma, colorectal cancer, mesothelioma, renal cancer, endometrial cancer, or lung cancer. The instant claims differ from the '251 claims in the dose (1500 $\mu g/m^2$) and the infusion time.

However, Riofrio *et al.* teaches an ET-743 dosage range of 600-1800 $\mu g/m^2$, specifically a dose of 1500 $\mu g/m^2$ administered by as a continuous *i.v.* infusion for 24 hours every 21 days for the treatment of advanced stage solid tumors such as colo-rectum, ovary, sarcoma, renal, breast, bladder, larynx, gastric, and ACUP cancers. "Advanced stage" tumors would reasonably include those tumors that are metastatic as recited in claim 31.

Accordingly, the claimed administration regimen would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. With respect to the specific

cancers recited in the dependent claims that are not explicitly recited in '251 or Riofrio *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that administration of 1500 μg/m^2 ET-473 administered as a continuous *i.v.* infusion for 24 hours every 21 days or 28 days would be effective given the broad spectrum of cancers recited in '251 and Riofrio *et al.* With respect to dexamethasone as recited in claims 35 and 47, Goodman and Gilman teach that that dexamethasone is effective as an antiemetic in cancer chemotherapeutic regimens (Tables on page 930). It is noted that nausea and vomiting are disclosed in Riofrio as a side effect of ET-743 therapy at doses above 600 μg/m^2. As such, the addition of dexamethasone to counter the nausea and vomiting elicited by ET-473 to the therapeutic methods of '251 would have been obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection.

Claims 12 and 28-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 (6/28/2007 claim set) of copending Application No. 11/769,873 in view of **Riofrio *et al.*** (23rd European Society for Medical Oncology Congress, Nov. 6-10, 1998, Abstract 639P). The claims of '873 are drawn a method of treating cancer in a human patient comprising administering ET 743 and dexamethasone (claim 1), wherein the patient has advanced and/or metastatic, previously treated cancer (claim 7), and wherein the cancer is sarcoma, ovarian cancer, breast cancer, melanoma, soft tissue sarcoma, or bone sarcoma (claims 9-14). The instant claims differ from the '873 claims in the dose (1500 μg/m^2) and the infusion time.

However, Riofrio *et al.* teaches an ET-743 dosage range of 600-1800 μg/m^2, specifically a dose of 1500 μg/m^2 administered by as a continuous *i.v.* infusion for 24 hours every 21 days for the treatment of advanced stage solid tumors such as colo-rectum, ovary, sarcoma, renal, breast, bladder, larynx, gastric, and ACUP cancers. "Advanced stage" tumors would reasonably include those tumors that are metastatic as recited in claim 31. Further, the disclosure of the '873 application is used as a dictionary to define the intended meaning of "administration" as recited in the '873 claims. In this regard, cyclic administration of ET 743 as a 24 hour

intravenous infusion in cycles of 3 or 4 weeks in doses of 500 to 1500 micrograms per m2 are disclosed (pages 10-11).

Accordingly, the claimed administration regimen would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. With respect to the specific cancers recited in the dependent claims that are not explicitly recited in '873 or Riofrio *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that administration of 1500 $\mu g/m^2$ ET-473 administered as a continuous *i.v.* infusion for 24 hours every 21 days or 28 days would be effective given the broad spectrum of cancers recited in '873 and Riofrio *et al.*

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614